AMENDMENTS TO THE SPECIFICATION SHOWING CHANGES

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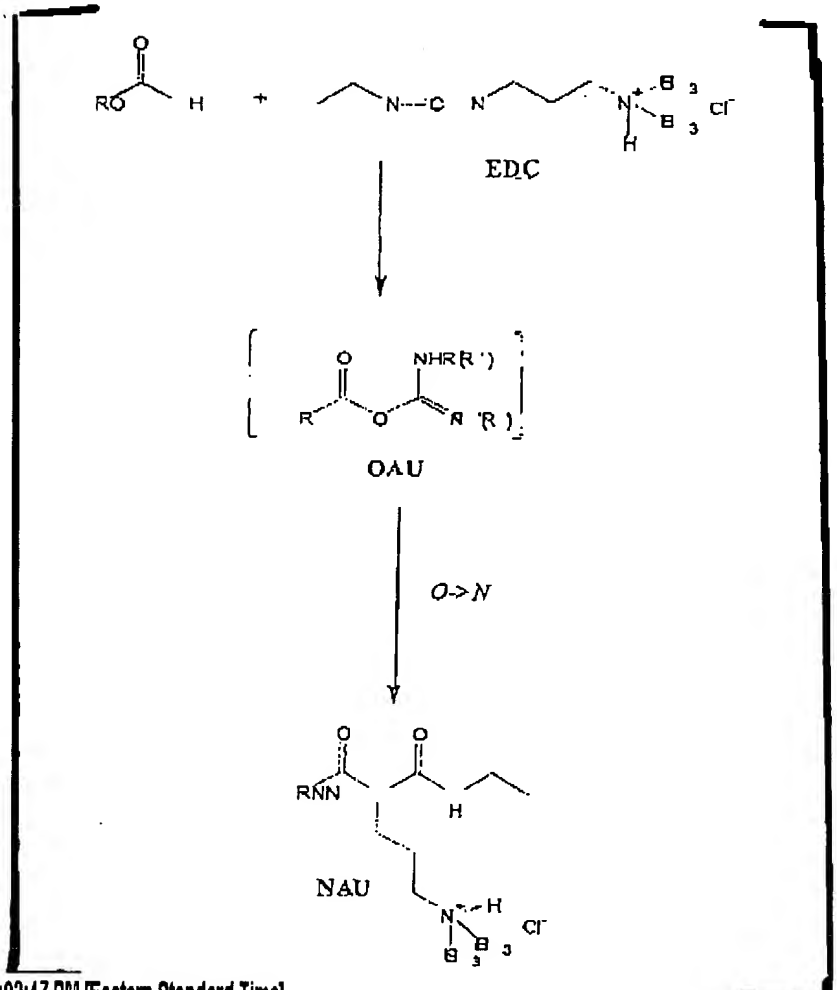
acid is advantageously in the range of from about 25,000 daltons to about 2,000,000 daltons.

Once the pH of the aqueous HA mixture has been adjusted, a carbodiimide is admixed with the HA. Preferred carbodiimides include EDC (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide or ETC (1-ethyl-3-(3-dimethylaminopropyl)) carbodiimide methiodide. EDC is soluble in water and is preferred.

The sequence and mode of addition of the reagents are not critical factors, but the ratio of the carbodiimide to HA is important. Best results are obtained when the ratio of carbodiimide to HA ranges from about 0.5:1 to 2:1. Lower ratios typically form more soluble products, while higher ratios typically result in soluble products.

In one embodiment, the derivatized HA/CMC gels of this invention are prepared by the reaction scheme shown below. As shown, HA/CMC is reacted with a derivatizing agent, such as the carbodiimide EDC, in the absence of a nucleophile.



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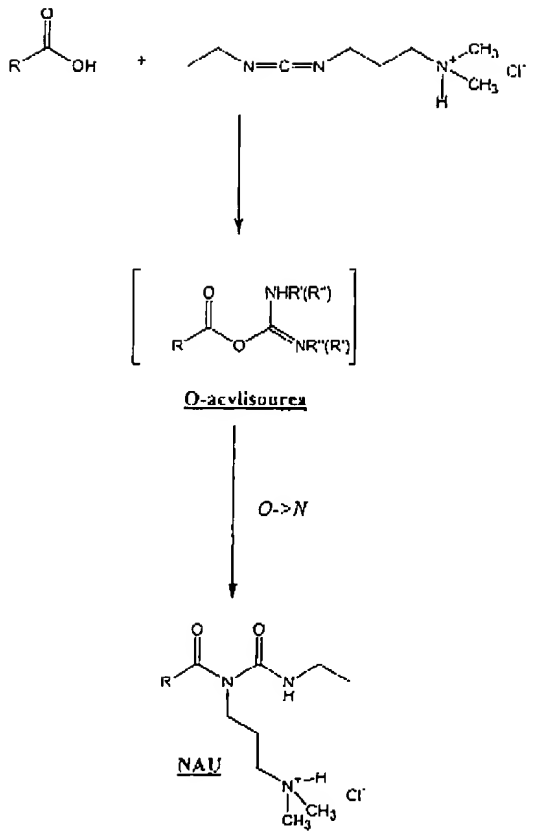

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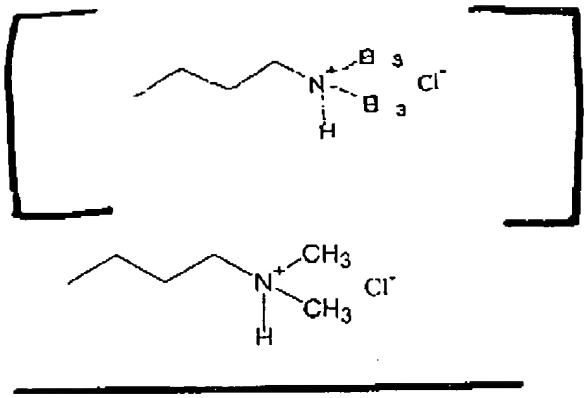
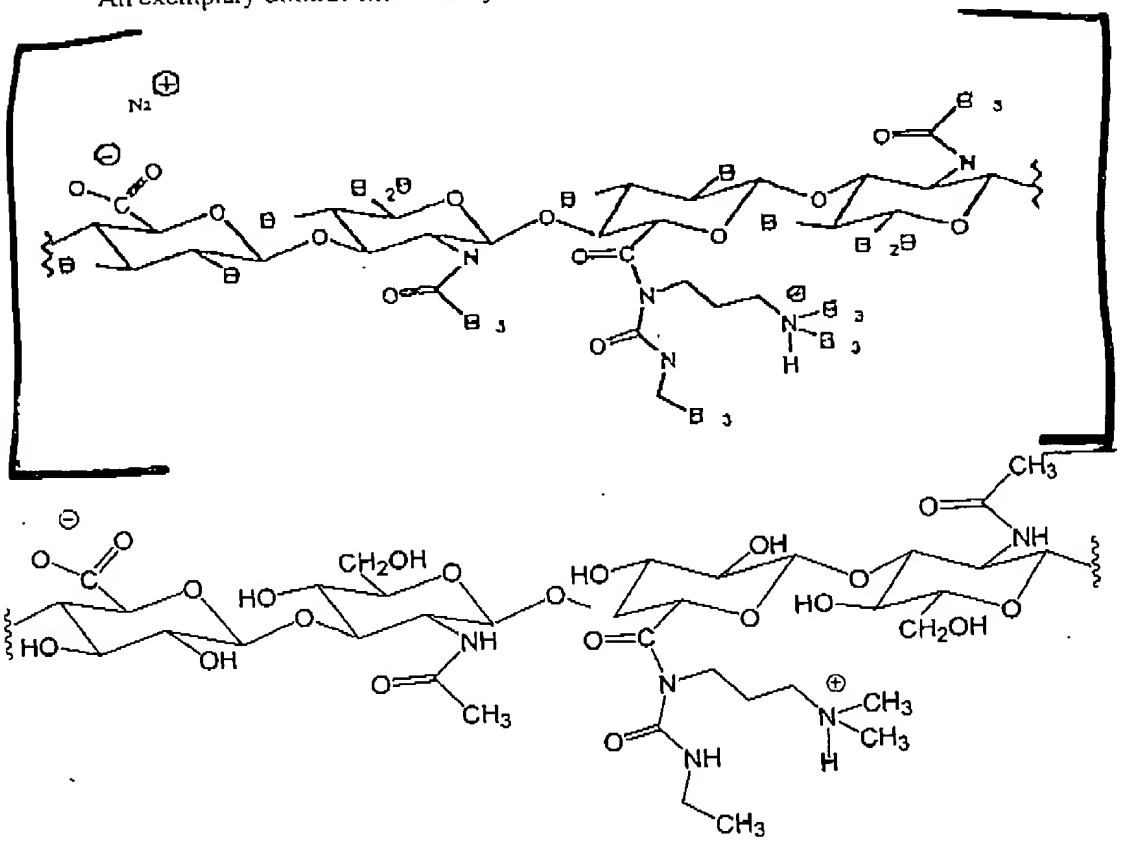
wherein R is HA or CMC, R' is Ethyl, and R" is



Normal reaction conditions can result in a 5% to 20% (molar basis) modification of the carboxyl groups on each polymer molecule. The carboxyl groups are both protonated and deprotonated, while the NAU modified groups are positively charged.

An exemplary diimide modified hyaluronic acid molecule is shown below:



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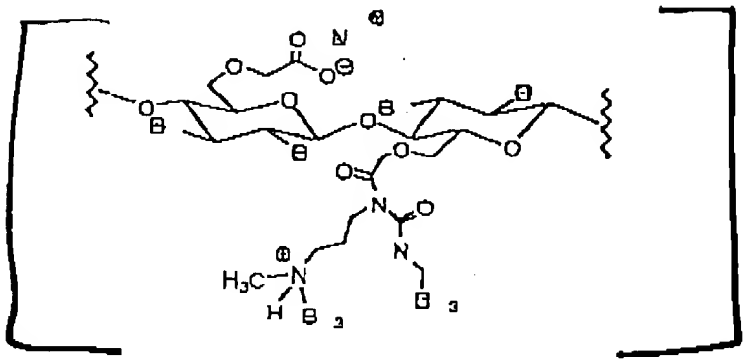
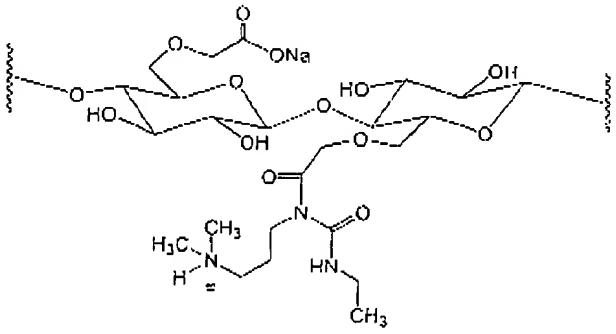
An exemplary diimide modified carboxymethylcellulose molecule is shown below:





The reaction product is a dried powder which can be dispersed in a buffered solution or physiological saline at concentrations of between 1% and 6% by weight. The product is capable of being terminally sterilized, which facilitates its storage and handling.

One particularly useful derivatized gel product is Sepragel®, a proprietary hyaluronic acid/carboxymethylcellulose gel product available from the Genzyme Corporation.

While not intending to be bound by any particular theory or mechanism, it is believed that the immunomodulating pharmaceutical compositions of the invention function in some aspects by inducing levels of IL-10. IL-10 is an anti-inflammatory cytokine that causes the down-regulation or inhibition of pro-inflammatory factors, cytokines, or cells. When the body encounters an inflammatory stimulus such as that which occurs with intra-abdominal infections, the elicitation of pro-inflammatory cytokines such as TNF-α is followed by the release of anti-inflammatory cytokines such

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as IL-10. IL-10 serves to dampen or mitigate the inflammatory process in order to maintain homeostasis and prevent excessive inflammation. In this manner, the invention provides methods for protecting against sepsis, adhesion formation, or excessive inflammation by the administration of each of these materials. It has also been discovered according to the invention that the immunomodulating pharmaceutical compositions of the invention function to prevent nitric oxide synthase (NOS) activity.

The anti-inflammatory effects of the compositions of the invention are particularly effective when the pharmaceutical composition is administered to the subject

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